DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

JUN 16 2010

The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Barton:

Thank you for your letter of April 30, 2010, cosigned by Ranking Member Michael Burgess, Subcommittee on Oversight and Investigations, regarding heparin.

The Food and Drug Administration (FDA or the Agency) has taken comprehensive steps to prevent contaminated heparin from entering the domestic drug market. For example, FDA designed test methods that identified the contaminant and then established and posted on the web test methods for analyzing heparin for this impurity. FDA also inspected both domestic finished dosage form facilities and international active pharmaceutical ingredient (API) suppliers to determine the presence and cause of the contamination, to map the supply route of contaminated products, and to gauge the inspected firms' compliance with current Good Manufacturing Practice (cGMP). FDA issued a sampling assignment to provide instructions to FDA staff about sampling and testing shipments of heparin sodium API. In addition, all shipments of heparin sodium API were examined upon entry. Beyond testing products upon entry, FDA has inspected and will continue to inspect firms that supply heparin to the United States. Through all of these actions, FDA has been carefully and diligently taking measures to preserve the availability of medically necessary heparin to U.S. patients and to ensure that the heparin is not contaminated.

We have responded below to your questions about FDA's investigation of the source of heparin contamination. Your questions are restated in bold, followed by our responses.

1. **What is FDA's strategy for solving the question of who caused the contamination of the heparin supply? Please detail the strategy and when it was developed, the names and positions of the FDA officials who developed the strategy, and the names and positions of the FDA officials responsible for implementing the strategy.**

As you know, at this point, FDA does not know who caused the contamination of the heparin API. Efforts to identify the perpetrators have been hampered by the fact that the contamination occurred in China. Many FDA components worked on various aspects of the contaminated heparin incident that came to our attention in January 2008, when investigators from the Centers for Disease Control and Prevention (CDC) were evaluating small clusters of adverse events in dialysis centers. FDA launched a far-ranging investigation in the United States and abroad to

contain the risk of contaminated heparin. Solving the question of who caused the contamination is an important issue for FDA; however, our initial primary focus was containing the risk from contaminated heparin to protect the public health. The key Offices/Centers leading the effort were the Center for Drug Evaluation and Research (CDER), Director, Janet Woodcock; the Office of Regulatory Affairs (ORA), Acting Associate Commissioner, Michael Chappell; and ORA's Office of Criminal Investigations (OCI), Director, Terry Vermillion. CDER and ORA assigned and conducted inspections, and developed test methodologies, to address the immediate need for ensuring the safety of the U.S. drug supply. OCI led the Agency's criminal investigation into the heparin contamination incident.

Once the pattern of adverse events was detected, our investigation soon led us to believe that the events were associated with contamination. In March 2008, FDA identified the contaminant responsible for the adverse events, oversulfated chondroitin sulfate (OSCS), an analog of heparin that is not readily detected by typical test methods. The Agency worked to develop, and posted on its website, test methods that allowed detection of the OSCS contaminant and concurrently initiated a sampling program to detect contaminated heparin products that might be introduced at our borders. FDA initiated inspections at Baxter International, Inc. (Baxter) sites in New Jersey and Illinois and other heparin manufacturers in the United States.

The Agency promptly contacted the Chinese government to initiate an inspection of Changzhou SPL Company, Ltd., the site that produced the API used in Baxter's contaminated drug products, issued a Warning Letter, and placed this site on Import Alert (IA) (to inform FDA field staff that the products are subject to detention without physical examination), based on the results of our inspection. Based on other inspections, the Agency placed other firms under IA in order to prevent the entry of other contaminated heparin shipments into the United States. Furthermore, FDA worked closely with the U.S. Pharmacopeia (USP) to include the enhanced test methods in the Heparin Sodium API monograph update of June 2008.

After identifying the contaminant, FDA performed numerous inspections in China focused on trying to determine if the contaminant was introduced at the inspected sites. Based on additional analytical testing, FDA uncovered the presence of the contaminant in crude heparin, which is the source material for manufacturing the heparin API. This evidence led FDA to believe that the contaminant had been intentionally introduced in the early stages of the crude heparin process, at least some of the time. The Agency initiated inspections of manufacturers of crude heparin in China but was denied full access to the manufacturing and laboratory facilities and not permitted to review records. FDA has been unsuccessful in getting cooperation from Chinese authorities to pursue the investigation beyond the API manufacturer. This has impeded FDA efforts to obtain information regarding the activities that took place at sites other than the API manufacturer.

FDA has repeatedly requested updates from the Chinese authorities regarding their investigation to identify those responsible for the heparin contamination, but these requests have yielded only general information. In addition, the Agency faced difficulties in obtaining records from the manufacturers of crude heparin and information from upstream firms, severely hampering our ability to perform an investigation. Nevertheless, to ensure the safety of the U.S. heparin supply, FDA screened and reviewed all imported heparin and worked with domestic manufacturers to analyze the heparin API used to manufacture finished products.

2. To what extent can FDA conduct a traceability investigation of various heparin supply chains in China on its own without the assistance of the Chinese government?

It would be very difficult, if not impossible, for FDA to conduct a criminal traceability investigation in China without the assistance of the Chinese government.

3. Assuming FDA could solve the case on its own, what would FDA do with this information?

If an FDA investigation uncovers criminal conduct, FDA would present this information to the Department of Justice for prosecution.

4. What actions is FDA taking to follow up on the Chongqing Imperial issues raised in this letter?

You expressed various concerns about FDA's investigation of Chongqing Imperial in pages 2-8 of your letter. We address these concerns below by referencing the corresponding heading in your letter.

a. Test results and investigative reports raise concerns (pp. 2-3)

You suggest that there is information warranting further investigation of Chongqing Imperial for direct involvement in, or knowledge about, the contamination of heparin. We will review the information provided in bullets 1–6 and decide if further investigation of Chongqing Imperial is warranted to determine its involvement or knowledge about the contamination of heparin.

b. Public information raises questions (p. 3)

Your letter raised the question of whether Canimperial Biopharma Inc. is a bogus front company, and whether it is used as a trans-shipment point for Chongqing's exports. FDA has checked Operational and Administrative System for Import Support (OASIS) data to determine what products have been imported into the United States by Canimperial Biopharma Inc. in Vancouver, British Columbia, Canada. Our review found no record of this firm in our Firm Establishment Identifiers table, indicating the firm Canimperial Biopharma Inc. has never been declared to FDA as a manufacturer or shipper for any importation of any type of FDA-regulated product.

FDA has verified that the web address *www.canimperial.com* is for Chongqing Imperial Bio-Chem Co. Ltd., located at 19-7 CITIC Bank Building, 5 Yanghe Sancun
Jiangbei District, Chongqing, 400020, China, with the following telephone and fax numbers in China and e-mail address for Mr. Richard Yin:

Telephone: (0086.23) 67635126, 67635612, 67635120
Fax: (0086.23)67635112
E-mail: richard08072002@yahoo.com
info@canimperial.com
imperial@onlin.cq.cn

This web address makes no reference to Canimperial Biopharma Inc. in Vancouver, British Columbia. We conducted a web search for the latter and found a reference to Canimperial Biopharma Inc; 3588 46th Ave., Vancouver, British Columbia, V5S 4T8 Canada at the web address: *http://www.naturalproductsinsider.com/Buyers-Guide.aspx?li=43626.* This web address includes the address for Chongqing Imperial Biochem Co., Ltd. (*www.canimperial.com*) and the contact information for Richard Yin, Marketing Manager (info@camimperial.com).

c. Export reports raise questions (p.4)

You note that export data reveals that in 2008 Chongqing Imperial was the third leading Chinese exporter of crude heparin. You question whether changes in export patterns raise the question of whether Chongqing Imperial was exporting to the United States under a different label. FDA has evaluated available Agency internal data to determine if there appears to be a pattern that raises concerns regarding importation to the United States under a different label. Our review found the number of shipments of declared heparin products from Chongqing Imperial China in Fiscal Year 2007 and Fiscal Year 2008 remained constant.

d. FDA's inspection report raises questions (pp.4-5)

Our review of the Chongqing September 22–25, 2008, inspection report revealed that the inspection team mistakenly reported the address of the firm it investigated. However, we do not feel that the inspectors were misinformed about the true identity and control of the Chongqing heparin manufacturing site.

We also reviewed IA # 66-40 (refer to FDA's website *http://www.accessdata.fda.gov/cms_ia/importalert_189.html*) and noticed a typographical error in a street address. FDA is correcting the address in the IA.

Inspection Issues Raised by FDA's Handling of Chongqing Imperial (pp.5-8)

As you noted, FDA has found it difficult and challenging to conduct inspections in the remote areas of China. FDA inspectors had difficulty accessing the facilities and had to rely heavily on translators from the company. You express concern that FDA did not adequately follow up on leads from this particular investigation, that FDA did not adequately investigate the supply chain, and that the establishment inspection report (EIR) raised questions about what heparin product the company was manufacturing.

FDA inspected Chongqing Imperial Bio-Chem Co., Ltd., a crude heparin sodium manufacturer, from September 22-25, 2008. This inspection was the initial inspection of this company. The inspection revealed objectionable conditions that FDA reported to the firm, which included,

among other things, lack of an ongoing stability program, no process water system in place, and analytical method concerns with the nuclear magnetic resonance (NMR) (which tests for product potency).

This was just one of several inspections in China. As noted previously in response to Question 1, given the difficulties in obtaining information, our ability to perform an adequate investigation has been severely hampered. It became clear that to ensure the safety of the U.S. heparin supply, FDA needed to focus its resources on screening and reviewing all imported heparin and working with domestic manufacturers to analyze the heparin API used to manufacture finished products. As discussed below, all APIs from this company are subject to an IA in the United States.

During the September 2008 establishment inspection at Chongqing Imperial Bio-Chem Co., Ltd., FDA determined another company was manufacturing crude heparin for Chongqing Imperial Bio-Chem Co., Ltd. As such, the locations for these related firms were identified as being responsible for the manufacture and/or distribution of adulterated heparin products, based on violative analytical results obtained at the time of importation into the United States. Based on the information obtained during the establishment inspection of Chongqing Imperial Bio-Chem Co., Ltd., FDA added all APIs, including but not limited to crude forms of APIs such as heparin, from both firms to IA #66-40: "Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMP's" on March 16, 2009. Thus, all APIs, including heparin, from both firms, are subject to detention without physical examination when offered for entry into the United States because the article(s) appears to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act or the Act) in that the methods and controls used in its manufacture and control do not appear to conform to cGMP.

These products will continue to be subject to detention without physical examination until adequate evidence is provided to remove the products from the IA, evidence that the conditions that gave rise to the apparent violation have been resolved and which gives FDA confidence that future entries will be in compliance with the Act.

The relationship between the firms, while known, is not specified in the alert and is not necessary for purposes of entry screening upon import into the United States. If heparin is offered for import into the United States from either Chongqing Imperial Bio-Chem Co., Ltd. or another company, the shipments will be flagged as being subject to detention without physical examination and handled according to FDA's established procedures.

Similarly, in July and August 2008, during establishment inspections at the Shanghai No. 1 Biochemical and Pharmaceutical Co., Ltd. Minhang location and Qingdao Jiulong Biopharmaceutical Co., FDA determined Qingdao Jiulong Biopharmaceutical Co. was manufacturing crude heparin for Shanghai No. 1 Biochemical and Pharmaceutical Co., Ltd. Both firms were identified as being responsible for the manufacture and/or distribution of adulterated heparin product and were added to IA #66-40 for all heparin products on January 21, 2009, to include Shanghai No. 1 Biochemical & Pharmaceutical Co., Ltd., at three locations in Shanghai (Minhang, Shangqui Road and Zhongxing Road).

Subsequently, based on the information obtained during the establishment inspections of Shanghai No. 1 Biochemical and Pharmaceutical Co., Ltd. (Minhang location) and Qingdao Jiulong Biopharmaceutical Co., CDER recommended all APIs, including but not limited to crude forms of APIs such as heparin, from both firms be included in IA #66-40: "Detention Without Physical Examination of Drugs From Firms Which Have not met Drug GMP's." FDA added all APIs from both firms to IA #66-40 on April 14, 2009.

Thus, all APIs, including heparin, from both Shanghai No. 1 Biochemical and Pharmaceutical Co., Ltd. (Minhang location) and Qingdao Jiulong Biopharmaceutical Co. are subject to detention without physical examination when offered for entry into the United States, because the article(s) appears to be adulterated within the meaning of section 501(a)(2)(B) of the Act in that the methods and controls do not appear to conform to cGMP.

5. Does the FDA agree there is a basis to make another request to the Chinese government about the heparin contamination investigation? If not, why not?

As mentioned in our response to Question 1, FDA has requested updates from the Chinese authorities regarding their investigation of the heparin contamination on several occasions. While China's State Food and Drug Administration (SFDA) has been responsive to inquiries from FDA, and has offered general information regarding matters that fall under its jurisdiction, the Agency has not received any substantive information to aid the investigation. The Chinese government claims to have no breakthroughs on determining the reasons of contamination: the raw material for heparin is from animal product processors who are not under SFDA jurisdiction; this type of processor is very small and is spread widely in rural areas; the raw materials are usually resold or reprocessed several times with no comprehensive and reliable records on the chain of distribution and process. With the opening of our China offices, FDA is working to increase communication and cooperation with Chinese authorities. We will continue to interact and collaborate with our regulatory counterparts in China in an effort to identify those responsible for the heparin contamination.

6. Is the FDA willing to cooperate and even share information with the Chinese government in an effort to solve the heparin contamination case? Would FDA be able to do so under current law and under the current agreement with the SFDA? If not, why not?

There is no legal impediment to FDA's cooperating with the Chinese government in the heparin contamination matter. However, with regard to sharing relevant information in its possession with SFDA, FDA is constrained by U.S. law, and its ability to share information with SFDA depends on the type of information involved.With regard to publicly available information (such as FDA Form 483s and redacted EIRs), information that is or could be made available to the public could also be made available to SFDA. With regard to trade secret information (such as details of manufacturing processes or formula), such information could only be disclosed to SFDA (or to any other recipient) with the consent of the owner of the information. (See, *e.g.*, 21 *United States Code* (U.S.C.) § 331(j); 18 U.S.C. § 1905; 21 *Code of Federal Regulations* (CFR) 20.61.)

With regard to confidential commercial information (such as identities of manufacturers' customers or suppliers), such information could be shared with SFDA with the consent of the owner of the information. Absent the owner's consent, confidential commercial information could be shared with SFDA only in accordance with the provisions of one of FDA's regulations, 21 CFR 20.89. This regulation provides that under certain preconditions, "[t]he Commissioner of Food and Drugs, or any other officer or employee of the [FDA] whom the Commissioner may designate to act on his or her behalf for the purpose, may authorize the disclosure of confidential commercial information submitted to the [FDA], or incorporated into agency-prepared records, to foreign government officials who perform counterpart functions to the [FDA] as part of cooperative law enforcement or regulatory efforts." (21 CFR 20.89(c)(1))

In order to share the information, the foreign government agency must have "provided both a written statement establishing its authority to protect confidential commercial information from public disclosure and a written commitment not to disclose any such information provided without the written permission of the sponsor or written confirmation by the [FDA] that the information no longer has confidential status." 21 CFR 20.89 (c)(1)(i). Furthermore, the Commissioner or designee must also make a determination that "[t]he sponsor of the product application has provided written authorization for the disclosure; [or that] [d]isclosure would be in the interest of public health by reason of the foreign government's possessing information concerning the safety, efficacy, or quality of a product or information concerning an investigation" (21 CFR 20.89(c)(1)(ii))

FDA does not have a Confidentiality Commitment from SFDA so we cannot legally share confidential commercial information with that Agency under 21 U.S.C. § 20.89.

The Agreement between the Department of Health and Human Services (HHS) and SFDA on the Safety of Drugs and Medical Devices does not provide for the exchange of confidential commercial information and does not meet the requirements of 21 CFR 20.89 that would authorize FDA to share this type of information with SFDA.

7. **Does FDA agree that the contamination of the heparin supply is an international issue? If so, why hasn't the FDA sought international support from the World Health Organization and/or other countries to get more transparency and cooperation from the Chinese government, or to provide assistance to the Chinese government, in the heparin contamination/source investigation?**

FDA agrees that the contamination of the heparin supply is an international issue. While we understand and appreciate that the World Health Organization (WHO) is a valuable international public health organization, they would not be the appropriate body to assist in investigating an incident such as this. They are not an enforcement organization and do not have the tools to assist in investigations. We do, however, engage regularly with the WHO on medical product anti-counterfeiting issues. This issue was on the agenda of the May 2010 World Health Assembly meeting in Geneva, where FDA was represented by Commissioner Margaret Hamburg and HHS Secretary Kathleen Sebelius. It should also be noted that we have collaborated and continue to collaborate with our international counterparts in investigating this incident. FDA conducted joint inspections of Chinese firms with our United Kingdom counterparts. We also

hosted two international meetings of global inspectorates, including representatives from the Chinese regulatory authority, to review the incident with an eye towards preventing future occurrences.

Thank you again for contacting us concerning this matter. If you have further questions, please let us know. We have sent the same letter to Ranking Member Michael Burgess.

Sincerely,

Jeanne Ireland

Jeanne Ireland
Assistant Commissioner
for Legislation